REMARKS

Claims 1-16 are pending in this application. Claims 5, 10 and 16 have been canceled. Claims 1, 6 and 11 have been amended. No new matter has been added by this amendment. Reconsideration of the pending claims is respectfully requested in view of the amendments and the following remarks.

I. Rejection of Claims under 35 U.S.C. §102(b)

The Examiner has rejected claims 1-16 under 35 U.S.C. §102(b) as being anticipated by Akagi et al. (U.S. Patent 5,723,269) hereinafter referred to as Akagi.

Applicants respectfully point out that Akagi teaches that aggregation of the microparticles can be prevented by the use of an aqueous solution of a water soluble inorganic acid, organic acid or salt of an organic acid sprayed from a separate source or nozzle onto a drug and polymer microparticle compound, see column 10 lines 3-19. Akagi does not teach a microsphere composition with a basic excipient incorporated into a biodegradable polymer to form a polymer matrix. Nor does Akagi teach that a drug is encapsulated by the polymer matrix wherein the basic excipient

comprises a bicarbonate which minimizes degradation of the drug, as claimed by the present invention.

To anticipate an invention the reference must teach every element of the claim under MPEP 2131. Thus Akagi cannot be held to anticipate the claims of the present invention. In an earnest effort to be completely responsive, however, the following argument addresses the Examiner's specific claim rejections with regard to the Akagi reference:

A. Claim 1

With respect to claim 1, it is suggested that the microparticles including microspheres produced by the process disclosed by Akagi comprise a drug entrapped in a biodegradable polymer and mixed with a pH adjustor, including a base such as sodium hydroxide. The limitation in the claims that the basic excipient minimizes degradation of a drug encapsulated within said microsphere by maintaining a near neutral pH environment within the microsphere" is suggested to be inherent to the composition. It is suggested that the prior art defines the basic excipient as pH adjustor and that the patent discloses a

biodegradable microsphere comprising a biodegradable polymer and a basic excipient as claimed by the present invention.

Applicants respectfully disagree.

As described above, unlike the present invention, Akagi clearly teaches a polymer/drug microparticle mixture (column 9, beginning at line 10) coated with a separate solution of an inorganic salt, organic acid, or salt of the organic acid.

In an earnest attempt to facilitate prosecution of this case and clarify the present invention, Applicants have amended claim 1 to recite that the modified biodegradable microsphere comprises (1) a basic excipient incorporated into a biodegradable polymer to form a polymer matrix; and

(2) a drug encapsulated by said polymer matrix. It is further clarified through amendment that the basic excipient comprises a bicarbonate. Support for this amendment is found throughout the specification and particularly at page 3, lines 29 through page 4, line 4; and page 12, line 34 through page 13, line 21.

Akagi cannot anticipate claim 1 of present invention as it does not teach all of the limitations of the present invention

namely that the drug is encapsulated by the polymer matrix comprising basic excipient incorporated into a biodegradable polymer. Nor does it teach that the basic excipient comprises a bicarbonate.

Withdrawal of this rejection is respectfully requested.

B. Claim 6

With respect to claim 6, it is suggested that Akagi provides a method to prepare microspheres comprising dissolving a drug in the presence of a pH adjuster including sodium hydroxide and mixing said solution with a polymer solution. Akagi is further suggested to contemplate the use of biodegradable polymers in the method of the invention. Akagi is suggested to teach that the microparticles provide a prolonged release of the drug and exhibit longer sustained effects as compared with the conventional sustained release drugs. It is suggested that Akagi teaches that both the drug and the basic excipient are incorporated into the polymer. It is suggested that the "comprising" language of the claim allows for any order in the additional of the various ingredients. The Examiner suggests that the limitation in the claim that "degradation of the drug

encapsulated within said microsphere is minimized by maintaining a near neutral pH environment within said microsphere" is inherent in the composition.

Applicants respectfully disagree.

However in an earnest attempt to facilitate prosecution and to clarify the invention, claim 6 has been amended to recite a method of improving the release profile of a drug encapsulated within a incorporating a basic excipient into a biodegradable polymer to form a polymer matrix and encapsulating the drug within the polymer matrix to form a microsphere so that degradation of the drug encapsulated within said microsphere is minimized by the basic excipient which comprises a bicarbonate. Support for this amendment is found throughout the specification and at pages 3-4 and 12-13.

Contrary to the Examiner's suggestions, Akagi does not teach all of the limitations of claim 6, namely Akagi does not teach that the drug is encapsulated within the polymer matrix. Nor that the polymer matrix is a basic excipient comprising a bicarbonate incorporated into a biodegradable polymer.

Thus, claim 6 is not anticipated by Akagi.

Withdrawal of this rejection is respectfully requested.

C. Claim 11

With respect to claim 11, Akagi is suggested to teach a method comprising encapsulating a drug and a basic pH adjuster in a biodegradable polymer and to further disclose administration of the preparations of the invention to a patient in need thereof. It is suggested that the Akagi patent teaches that both the drug and the basic excipient are encapsulated into the polymer. The Examiner suggests that the comprising language of claim 11 allows for any order in the addition of the various ingredients. Furthermore, in Example 6, in the specification, a solution containing insulin and sodium bicarbonate is suspended in the polymer solution thus it is suggested that the method disclosed by Applicant is anticipated. It is suggested that the limitation "basic excipient minimizes degradation of a drug encapsulated within said microsphere by maintaining a near neutral pH environment within the microsphere" is inherent to the composition.

Applicants respectfully disagree.

It is respectfully pointed out that claim 11 has been amended to clarify the method of the invention and recite encapsulating the drug in a biodegradable polymer matrix comprising a basic excipient incorporated into a biodegradable polymer to form a polymer microsphere wherein said basic excipient comprises a bicarbonate which minimizes degradation of the drug encapsulated within said microsphere. Support for this amendment is found throughout the specification and at pages 12-13 and page 14, line 10. As set forth *supra,* Akagi does not teach that the drug is encapsulated within a polymer matrix comprising a basic excipient incorporated into a biodegradable polymer. Neither does Akagi teach that the excipient comprises a bicarbonate. As Akagi does not teach all of the limitations of claims 11, it cannot be held to anticipate the present invention.

Withdrawal of this rejection is respectfully requested.

D. Claims 2, 3, 7, 8, 13 and 14

With regard to claims 2, 3, 7, 8, 13 and 14 it is suggested that Akagi et al. includes peptides having biological activity and specifically insulin among the drugs used on the invention.

Applicants respectfully disagree.

Claims 2, 3, 7, 8, 13 and 14 are dependent upon claim 1. As recited above Akagi does not anticipate or suggest claim 1, therefore the dependent claims are not anticipated or suggested.

Withdrawal of this rejection is respectfully requested.

E. Claims 4, 9 and 15

With respect to claims 4, 9 and 15, it is suggested that Akagi et al. includes a copolymer of lactic acid and glycolic acid among the biodegradable polymers suitable for the invention.

Applicants respectfully disagree.

Claims 4, 9 and 15 are dependent upon claim 1. As recited above Akagi does not anticipate or suggest claim 1, therefore the dependent claims are not anticipated or suggested.

Withdrawal of this rejection is respectfully requested.

F. Claim 12

With respect to claim 12, it is suggested that Akagi contemplates the parenteral administration of the composition prepared by the method of the invention.

Applicants respectfully disagree.

Claim 12 is dependent upon claim 11. As recited above Akagi does not anticipate or suggest claim 11, therefore the dependent claims are not anticipated or suggested.

Withdrawal of these rejections and allowance of the pending claims is respectfully requested.

II. Rejection of Claims under 35 U.S.C. §102(e) relating to Steiner

The Examiner has rejected claims 1-16 under 35 U.S.C. §102(e) as being anticipated by Steiner et al. (U.S. Patent 6,428,771), hereinafter referred to as Steiner.

Applicants respectfully submit that Steiner teaches a method of drug delivery to the pulmonary system using a drug within a polymer to form a microparticle (as defined in column 2). Steiner teaches that diketopiperazines are structural elements form microparticles with desirable size distributions, column 3, lines 50-53. Steiner teaches the use of bicarbonate or other non-basic solution for dissolving a diketopiperazine side chain (column 8, lines 20-40) so that symmetrical diketopiperazine derivatives are formed, see column 7 lines 5 through column 8

lines 50. The diketopiperazines may also be used for radiolabeling, column 6, line 63 through column 7, line 4. The bicarbonate is also taught to be useful in precipitating the microparticle (column 8, lines 31-33). Steiner does not teach the use of a polymer matrix comprising a basic excipient incorporated into a biodegradable polymer, wherein the polymer matrix encapsulates a drug. Further, Steiner does not teach that the excipient comprises a bicarbonate to minimizes degradation of a drug encapsulated within a microsphere.

In an attempt to facilitate prosecution of this application and clarify the invention and recite that the basic excipient is incorporated into a biodegradable polymer to form a polymer matrix. Claims 1, 6 and 11 have been further amended to recite the limitation of claims 5, 10 and 16 namely that the excipient comprises a bicarbonate. Steiner can not be held to anticipate the present invention as Steiner does not teach every limitation.

In an earnest effort to be completely responsive, the following argument addresses the Examiner's specific claim rejections with regard to the Steiner reference:

A. Claim 1

With respect to claim 1, Steiner is suggested to teach a drug encapsulated in the microparticle of the invention by adding the drug to a solution comprising the biodegradable polymer and bicarbonate, so that the particles dissociate at physiological pH. It is suggested that the limitation "basic excipient minimizes degradation of a drug encapsulated within said microsphere by maintaining a near neutral pH environment within the microsphere" is inherent to the composition. Steiner is suggested to provide a biodegradable microsphere for encapsulation of a drug comprising a biodegradable polymer and a basic excipient, as claimed by Applicants.

Applicants respectfully disagree.

As discussed *supra,* Steiner does not teach all of the limitations of the present invention, namely Steiner fails to teach a polymer matrix comprising a basic excipient and a biodegradable polymer which is used to coat a drug. Similarly Steiner fails to teach an excipient which comprises a bicarbonate is a required component in the polymer matrix. Thus, Steiner does not anticipate the present invention.

Withdrawal of this claim is respectfully requested.

B. Claim 6

With respect to claim 6, it is suggested that Steiner et al. provides a method comprising adding the drug to be encapsulated to a solution comprising the biodegradable polymer and bicarbonate and teaches that the method of the invention provides improved microparticles which biodegrade at physiological pH and can be delivered to targeted locations. It is suggested that "degradation of the drug encapsulated within said microsphere is minimized by maintaining a near neutral pH environment within said microsphere" is inherent to the composition.

Applicants respectfully disagree.

As discussed *supra,* Steiner does not teach all of the limitations of the present invention. The bicarbonate taught by Steiner is not a component of a polymer matrix which encapsulates a drug. Thus, Steiner does not anticipate the present invention.

Withdrawal of this rejection is respectfully requested.

C. Claim 11

With respect to claim 11, it is suggested that Steiner et al. teach that the drug is encapsulated in microparticles by

dissolving a biodegradable polymer in bicarbonate and adding the drug to the polymer solution, and the microparticles thus obtained can be delivered to a patient using a variety of methods. It is suggested that the limitation "basic excipient minimizes degradation of a drug encapsulated within said microsphere by maintaining a near neutral pH environment within the microsphere" is inherent to the composition.

Applicants respectfully disagree.

As discussed *supra,* Steiner does not teach all of the limitations of claim 11 of the present invention, namely the polymer matrix comprising a basic excipient incorporated into a biodegradable polymer is not taught. Thus, Steiner does not anticipate the present invention.

Withdrawal of this rejection is respectfully requested.

D. Claims 2, 3, 7, 8, 13 and 14

With respect to claim 2, 3, 7, 8, 13 and 14 it is suggested that Steiner includes proteins or peptides such as insulin among the drugs encapsulated in the microspheres of the invention.

Applicants respectfully disagree.

Claims 2, 3, 7, 8, 13 and 14 are dependent upon claim 1. As recited above Steiner does not anticipate or suggest claim 1, therefore the dependent claims are not anticipated or suggested.

Withdrawal of this rejection is respectfully requested.

E. Claims 4, 9, and 15

With respect to claims 4, 9, and 15, it is suggested that Steiner includes poly(lactic acid), poly(glycolic acid) and copolymers thereof among the biodegradable polymers used in the inventions (see column 3, line 7-9).

Applicants respectfully disagree.

Claims 4, 9, and 15 are dependent upon claims 1, 6 and 11. As recited above Steiner does not anticipate or suggest claims 1, 6 or 11, therefore the dependent claims are not anticipated or suggested.

Withdrawal of this rejection is respectfully requested.

F. Claims 5, 10 and 16

With respect to claims 5, 10 and 16, it is suggested that Steiner et al. provide a method of encapsulating a drug in a microsphere comprising the step of dissolving the biodegradable polymer in bicarbonate and a composition comprising bicarbonate.

Applicants respectfully disagree.

Claims 5, 10 and 16, are dependent upon claims 1 and 6. As recited above Steiner does not anticipate or suggest claim 1 or 6, therefore the dependent claims are not anticipated or suggested. Furthermore, claims 5, 10 and 16 have been canceled thereby mooting this rejection.

Withdrawal of this rejection is respectfully requested.

G. Claim 12

With respect to claim 12, Steiner includes administration of the compositions of the invention into the nasal passages among the methods of delivery used in the invention. Nasal administration is a form of parenteral delivery as claimed by Applicant.

Applicants respectfully disagree.

Claim 12 is dependent upon claim 11, as set forth in detail above, Steiner can not be held to anticipate claim 11, and therefore dependent claim 12 is not anticipated or suggested.

Withdrawal of this rejection is respectfully requested.

III. Rejection of Claims under 35 U.S.C. §102(e) relating to Bernstein et al.

Claims 1, 2, 4, 6, 7, 9 11-13 are rejected under 35 U.S.C. 102(e) as being anticipated by Bernstein et al. (U.S. Patent 5,912,015) hereinafter referred to as Bernstein. It is suggested that Bernstein discloses compositions comprising a polymeric matrix, a biologically active agent dispersed within the matrix and a metal cation also dispersed in the matrix

As set forth *supra* it is respectfully pointed out that claims 5, 10 and 16 are not anticipated by Bernstein. In an earnest attempt to facilitate prosecution of this application and clarify the invention, claims 1 and 11 have been amended to recite the limitation of claims 5, 10 and 16 namely that the excipient comprises a bicarbonate. Bernstein can not be held to anticipate the present invention as Bernstein does not teach every limitation, namely that the excipient comprises a bicarbonate. In an earnest effort to be completely responsive however, the following argument is provided to address the Examiner's specific claim rejections with regard to the Bernstein reference:

A. Claim 1

With respect to claim 1, it is suggested that Bernstein provides a microparticle having the shape of a sphere and comprising an active agent and a metal cation dispersed in the polymer matrix, and teaches that biodegradable polymers are preferred. Bernstein is suggested to teach that microspheres of PLGA degrade *in vivo* and *in vitro* and are formed using zinc carbonate a basic excipient as metal cation. It is suggested that the limitation "basic excipient minimizes degradation of a drug encapsulated within said microsphere by maintaining a near neutral pH environment within the microsphere" is inherent to the composition. Thus, it is suggested that Bernstein provides a biodegradable microsphere for encapsulation of a drug comprising a biodegradable polymer and a basic excipient, as claimed by the Applicant.

Applicants respectfully disagree.

As discussed *supra,* claim 1 has been amended to clarify the invention and teach that the basic excipient comprises bicarbonate. Bernstein does not teach all of the limitations of the present invention, namely that the excipient comprises a

bicarbonate. Thus, Bernstein does not anticipate the present invention.

Withdrawal of this rejection is respectfully requested.

B. Claim 6

With regard to claim 6, Bernstein is suggested to provide a method for modulating the release of an active agent and enhancing the control of the level of active agent released *in vivo* comprising the steps of dispersing a metal cation and the active agent in the polymer matrix for forming biodegradable microspheres encapsulating the active agent. It is suggested that the limitation "degradation of the drug encapsulated within said microsphere is minimized by maintaining a near neutral pH environment within said microsphere" is inherent to the composition.

Applicants respectfully disagree.

As discussed *supra,* claim 6 has been amended to recite that the excipient comprises bicarbonate, as supported on page 14, line 9-14. Bernstein does not teach this limitation. Thus, Bernstein does not anticipate the present invention.

Withdrawal of this rejection is respectfully requested.

C. Claim 11

With respect to claim 11, Bernstein is suggested to teach the microspheres comprising an active agent encapsulated in a biodegradable polymer comprising a basic excipient are administered to a patient. It is suggested that the limitation "basic excipient minimizes degradation of a drug encapsulated within said microsphere by maintaining a near neutral pH environment within the microsphere" is inherent to the composition.

Applicants respectfully disagree.

As discussed *supra,* claim 11 has been amended to clarify the present invention and recite that the excipient comprises a bicarbonate. Thus, Bernstein does not teach all of the limitations of the present invention. Accordingly, Bernstein does not anticipate the present invention.

Withdrawal of this rejection is respectfully requested.

D. Claims 2, 7, and 13

With respect to claims 2, 7, and 13, it is suggested that Bernstein teaches that the microspheres of the invention encapsulate a protein.

Applicants respectfully disagree.

Claims 2, 7, and 13 are dependent upon claim 1. As recited above Bernstein does not anticipate or suggest claim 1, therefore the dependent claims are not anticipated or suggested.

Withdrawal of this rejection is respectfully requested.

E. Claims 4, 9, and 15

With respect to claims 4, 9, and 15, it is suggested that Bernstein discloses PLGA microspheres.

Applicants respectfully disagree.

Claims 4, 9 and 15 are dependent from claims 1, 6 and 11 respectfully. As set forth fully above, claims 1, 6 and 11 are not anticipated by Bernstein. Accordingly the claims dependent from 1, 6 and 11 cannot be anticipated by Bernstein.

Withdrawal of this rejection is respectfully requested.

F. Claim 12

With respect to claim 12 it is suggested that Bernstein et al teach that the microspheres of the invention are administered parenterally by injection.

Applicants respectfully disagree. Claim 12 is dependent from claim 11. As set forth fully above, claim 11 cannot be

anticipated by Bernstein. Accordingly claim 12, dependent from 11 is not anticipated by Bernstein.

Withdrawal of this rejection is respectfully requested.

IV. Rejection of Claims under 35 U.S.C. §102(a) relating to Steiner

The Examiner has rejected claims 1-16 under 35 U.S.C. §102(a) as being anticipated by Steiner et al (U.S. Patent 6,428,771).

Under MPEP 2131 " a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior are reference" *Verdegaal Bros v. Union Oil Co. of California* 2 USPQ2d 1051, 1053 (Fed. Cir 1987) "The identical invention must be shown in complete detail as is contained in the …claim" *Richardson v Suzuki Motor Co.* 9 USPQ2 1913, 1920 (Fed Cir 1989).

Steiner does not teach a polymer matrix comprising a basic excipient incorporated into a biodegradable polymer to form a polymer matrix which encapsulates a drug. Rather, Steiner teaches that diketopiperazine with acidic side chains can be

dissolved with a bicarbonate (see column 8, lines 21-25) to deprotect side chains.

In an earnest attempt to facilitate prosecution of this application and clarify the invention, claims 1, 6 and 11 have been amended to recite the limitation of claims 5, 10 and 16, namely that the excipient comprises a bicarbonate. Steiner can not be held to anticipate the present invention as Steiner does not teach every limitation. Steiner does not teach the use of a polymer matrix comprising a basic excipient incorporated into a biodegradable polymer, wherein the polymer matrix encapsulates a drug. Further, Steiner does not teach that the excipient comprises a bicarbonate which minimizes degradation of a drug encapsulated within a microsphere. A set forth fully above, Steiner teaches a method of drug delivery to the pulmonary system using a drug within a polymer to form a microparticle (as defined in column 2). Steiner teaches the use of bicarbonate or other non-basic solution for dissolving a diketopiperazine side chain. See section II above for full argument. The following argument is provided to address the Examiner's specific claim rejections with regard to the Steiner reference:

A. Claim 1

With respect to claim 1, Steiner is suggested to teach microspheres made from biodegradable polymer and comprising a drug. With respect to claim 1, Steiner is suggested to teach that the drug is encapsulated in the microparticles of the invention by adding the drug to a solution comprising the biodegradable polymer and bicarbonate and the particles dissociate at physiological pH and can be delivered to targeted locations. It is suggested that the limitation "basic excipient minimizes degradation of a drug encapsulated within said microsphere by maintaining a near neutral pH environment within the microsphere" is inherent to the composition. Thus, it is suggested that Steiner et al. discloses a method of improving the release profile of a drug encapsulated in a biodegradable microsphere.

Applicants respectfully disagree.

As discussed *supra*, Steiner does not teach all of the limitations of claim 1 of the present invention, namely that polymer and bicarbonate are components of the polymer matrix used

to encapsulate a drug. Thus, Steiner does not anticipate the present invention.

Withdrawal of this rejection is respectfully requested.

B. Claim 6

With respect to claim 6, it is suggested that Steiner provides a method comprising adding the drug to be encapsulated to a solution comprising the biodegradable polymer and bicarbonate and teaches that the method of the invention provides improved microparticles which biodegrade at physiological pH and can be delivered to targeted locations. The limitation in the claims that "degradation of the drug encapsulated within said microsphere is minimized by maintaining a near neutral pH environment within said microsphere" is suggested to be inherent to the composition. It is suggested that Steiner discloses a method of improving the release profile of a drug encapsulated in a biodegradable microsphere as claimed by Applicants.

Applicants respectfully disagree.

As discussed *supra*, Steiner does not teach all of the limitations of claim 6 of the present invention. Steiner does not teach encapsulating the drug with a polymer matrix comprising

biodegradable polymer and bicarbonate. Thus, Steiner does not anticipate the present invention.

Withdrawal of this rejection is respectfully requested.

C. Claim 11

With respect to claim 11, it is suggested that Steiner teaches that the drug is encapsulated in microparticles by dissolving a biodegradable polymer in bicarbonate and adding the drug to the polymer solution, and the microparticles thus obtained can be delivered to a patient using a variety of methods. It is suggested that the limitation "basic excipient minimizes degradation of a drug encapsulated within said microsphere by maintaining a near neutral pH environment within the microsphere" is inherent to the composition.

Applicants respectfully disagree.

As fully described *supra,* Steiner does not teach all of the limitations of the present invention. The bicarbonate taught by Steiner is not a part of a polymer matrix used to encapsulate a drug. The bicarbonate of Steiner is used to deprotect diketopiperazines. Thus, Steiner does not anticipate the present invention.

Withdrawal of this rejection is respectfully requested.

D. Claims 2, 3, 7, 8, 13 and 14

With respect to claim 2, 3, 7, 8, 13 and 14 it is suggested that Steiner includes proteins or peptides such as insulin among the drugs encapsulated in the microspheres of the invention.

Applicants respectfully disagree.

Claims 2, 3, 7, 8, 13 and 14 are dependent upon claims 1, 6 and 11. As recited above Steiner does not anticipate or suggest claim 1, therefore the dependent claims are not anticipated or suggested.

Withdrawal of this rejection is respectfully requested.

E. Claims 4, 9, and 15

With respect to claims 4, 9, and 15, Steiner is suggested to teach poly(lactic acid), poly(glycolic acid) and copolymers thereof among the biodegradable polymers used in the inventions (see col 3, line 7-9), and thus anticipate the present invention.

Applicants respectfully disagree. Claims 4, 9, and 15 are dependent upon claims 1, 6 and 11. As recited above Steiner does not anticipate or suggest claims 1, 6 or 11 therefore the dependent claims are not anticipated or suggested.

Withdrawal of this rejection is respectfully requested.

F. Claims 5, 10 and 16

With respect to claims 5, 10 and 16, it is suggested that Steiner et al. provides a method of encapsulating a drug in a microsphere comprising the step of dissolving the biodegradable polymer in bicarbonate and a composition comprising bicarbonate.

Applicants respectfully disagree.

Steiner does not teach a polymer matrix comprising a basic excipient incorporated into a biodegradable polymer, wherein the polymer matrix is used to encapsulate a drug. Rather, Steiner teaches that diketopiperazine with acidic side chains can be dissolved with a bicarbonate (see column 8, lines 21-25) to deprotect side chains. However, claims 5, 10 and 16 have been canceled in prosecution of this application as recited supra in this paper thereby mooting this rejection.

Withdrawal of this rejection is respectfully requested.

G. Claim 12

With respect to claim 12, Steiner includes administration of the compositions of the invention into the nasal passages among the methods of delivery used in the invention. Nasal

administration is a form of parenteral delivery as claimed by Applicants.

Applicants respectfully disagree. Claim 12 is dependent upon claim 11, as set forth in detail above, Steiner can not be held to anticipate claim 11, and therefore, dependent claim 12 is not anticipated or suggested.

Withdrawal of this rejection is respectfully requested.

V. Rejection of Claims under 35 U.S.C. §102(a) relating to Bernstein

Claims 1, 2, 4, 6, 7, 9, 11-13 and 15 are rejected under 35 U.S.C. 102(a) as being anticipated by Bernstein et al. (U.S. Patent 5,912,015), hereinafter Bernstein.

As set forth *supra* it is respectfully pointed out the Examiner has acknowledged that claims 5, 10 and 16 are not anticipated by Bernstein. In an earnest attempt to facilitate prosecution of this application and clarify the invention, claims 1, 6 and 11 have been amended to recite the limitation of claims 5, 10 and 16 namely that the excipient comprises a bicarbonate. Bernstein can not be held to anticipate the present invention as

Bernstein does not teach every limitation, namely that the excipient comprises a bicarbonate. The following argument is provided to address the Examiner's specific claim rejections with regard to the Bernstein reference:

A. Claim 1

With respect to claim 1, it is suggested that Bernstein provides a microparticle having the shape of a sphere and comprising an active agent and a metal cation dispersed in the polymer matrix, and teaches that biodegradable polymers are preferred. Bernstein is suggested to teach that microspheres of PLGA degrade *in vivo* and *in vitro* and are formed using zinc carbonate a basic excipient as metal cation. It is suggested that the limitation "basic excipient minimizes degradation of a drug encapsulated within said microsphere by maintaining a near neutral pH environment within the microsphere" is inherent to the composition. Thus, Bernstein is suggested to provide a biodegradable microsphere for encapsulation of a drug comprising a biodegradable polymer and a basic excipient, as claimed by Applicants.

Applicants respectfully disagree.

As discussed *supra,* Bernstein does not teach all of the limitations of claim 1 of the present invention, namely that the excipient comprise a bicarbonate. Thus, Bernstein does not anticipate the present invention.

Withdrawal of this rejection is respectfully requested.

B. Claim 6

With respect to claim 6, Bernstein is suggested to provide a method for modulating the release of an active agent and enhancing the control of the level of active agent released *in vivo* comprising the steps of dispersing a metal cation and the active agent in the polymer matrix for forming biodegradable microspheres encapsulating the active agent. The limitation in the claims that "degradation of the drug encapsulated within said microsphere is minimized by maintaining a near neutral pH environment within said microsphere" is suggested to inherent to the composition.

Applicants respectfully disagree.

As discussed *supra,* Bernstein does not teach all of the limitations of the present invention, namely that the excipient

comprise a bicarbonate. Thus, Bernstein et al. do not anticipate the present invention.

Withdrawal of this rejection is respectfully requested.

C. Claim 11

With respect to claim 11, Bernstein is suggested to teach the microspheres comprising an active agent encapsulated in a biodegradable polymer comprising a basic excipient are administered to a patient. It is suggested that the limitation "basic excipient minimizes degradation of a drug encapsulated within said microsphere by maintaining a near neutral pH environment within the microsphere" is inherent to the composition.

Applicants respectfully disagree.

As discussed *supra,* Bernstein does not teach all of the limitations of the present invention, namely that the excipient comprise a bicarbonate. Thus, Bernstein does not anticipate the present invention.

Withdrawal of this rejection is respectfully requested.

D. Claims 2, 7, and 13

With respect to claims 2, 7, and 13, it is suggested that Bernstein teaches that the microspheres of the invention encapsulate a protein.

Applicants respectfully disagree.

Claims 2, 7, and 13 are dependent from claims 1, 6 and 11 which are not anticipated by Bernstein as set forth fully *supra*. Thus, claims 2, 7, and 13 can not be anticipated by Bernstein.

Withdrawal of this rejection is respectfully requested.

E. Claims 4, 9, and 15

With respect to claims 4, 9, and 15, it is suggested that Bernstein discloses PLGA microspheres.

Applicants respectfully disagree. Claims 4, 9 and 15 are dependent from claims 1, 6 and 11 respectfully. As set forth fully above, claims 1, 6 and 11 are not anticipated by Bernstein. Accordingly the claims dependent from 1, 6 and 11 cannot be anticipated by Bernstein.

Withdrawal of this rejection is respectfully requested.

F. Claim 12

With respect to claim 12 it is suggested that Bernstein teach that the microspheres of the invention are administered parenterally by injection.

Applicants respectfully disagree. Claim 12 is dependent from claim 11. As set forth fully above, claim 11 can not be anticipated by Bernstein. Accordingly claim 12, dependent from 11 is not anticipated by Bernstein.

Withdrawal of this rejection is respectfully requested.

Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly,

favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

Jane Massey Licata
Registration No. 32,257

Date: **June 24, 2004**

Licata & Tyrrell P.C.
66 E. Main Street
Marlton, New Jersey 08053

(856) 810-1515